PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4498PTWO/fe	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/11239	International filing date *(day/month/year)* 10.10.2003	Priority date *(day/month/year)* 18.10.2002
International Patent Classification (IPC) or both national classification and IPC C08B37/00		
Applicant FIDIA FARMACEUTICI S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.05.2004	01.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Grassi, D Telephone No. +49 89 2399-8499

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/11239

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-41 as originally filed

Claims, Numbers

1-73 as originally filed

Drawings, Figures

1-4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-26,32-34,37-55(all part) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-26,32-34,37-55(all part)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-26,32-34,37-55(all part)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26,32-34,37-55(all part)
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: Lou et al., Bioconjugate Chem. 1999, 10, 755-762 (cited in the application).
D2: SPARER R. V. ET AL.: "Controlled Release from Glycosaminoglycan Drug Complexes" in "Controlled Release Delivery Systems" 1983, MARCEL DEKKER , NEW YORK, p. 107-119

Re Item IV
The International Examining Authority found multiple (groups of) inventions in this international application. No required additional examination fees were paid by the applicant. Consequently, this Written Opinion is restricted to the first invention (cf. below).

The closest state of the art for the present application is represented by D1. It discloses a HA-Taxol conjugate wherein the covalent bond is formed between hydroxyl groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer comprising hydrazide groups.

The technical problem underlying the present claims is seen in the provision of alternative conjugates of taxol conjugates with hyaluronic acid.

In view of the disclosure of D1 the alternative solutions claimed do not share a common special technical feature as required by Rule 13.2 PCT and the fact that the present proviso of claim 1 excludes the conjugate of D1 cannot establish unity among the different alternatives.

The following inventions appear to be present:

a-1) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer, the bond between the spacer and the carboxyl groups of hyaluronic acid being an ester bond (cf. claims: 1-26, 32-34, 37-55, all part).

a-2) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer, the bond between the spacer and the carboxyl groups of hyaluronic acid being amide bond (cf. claims 1 and 27).

b) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and carboxyl groups of the hyaluronic acid without spacer.

c) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and OH groups of the hyaluronic acid.

d) Conjugate according to claim 1 in which the bond is formed between OH groups of the taxane and amino groups of deacetylated hyaluronic acid.

Re Item V

1) The subject-matter of present claims 1-26, 32-34, 37-55 (all part) is new (Article 33(2) PCT).

D1 discloses a HA-Taxol conjugate wherein the covalent bond is formed between hydroxyl groups of the taxane and carboxyl groups of the hyaluronic acid by means of a spacer comprising hydrazide groups. The present claims differ from D1 in that the bond between the spacer and the carboxyl groups of hyaluronic acid is an ester bond and not an (acid) hydrazide bond.

2) The subject-matter of claims 1-26, 32-34, 37-55 (all part) involves an inventive step (Article 33(3) PCT).

The closest state of the art for the present application is represented by D1 (cf. above).

The technical problem underlying the present claims is seen in the provision of alternative conjugates of taxol derivatives with hyaluronic acid.
In view of the test results (cf. page 35), the problem appears to be solved.

D2 discloses an other modified hyaluronic acid derivative in which the drug chloramphenicol is covalently attached to hyaluronic acid via amide linkage including an alanine bridge as an intermediate linking group (cf. page 111). The combination of D1 with D2 does not prompt the skilled person to the present conjugates involving a linker and an ester bond to HA. Consequently, inventive

activity appears to be present.